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Addition of Carbamoylsilanes to Electrophilically Substituted Alkenes. Preparation of β-Functionalized Tertiary Amides

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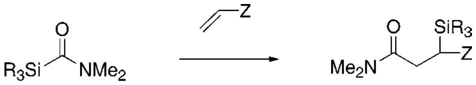
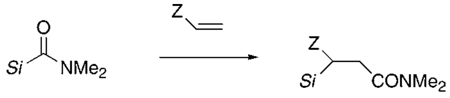
ABSTRACT



$Z = CO_2R, COR, CN, CF_3, NO_2, S(O)_2Et, P(O)(OEt)_2$

The Si–C bond of *N*,*N*-dimethylcarbamoylsilanes added regiospecifically to the C═C bond of electrophilically functionalized alkenes to afford β-silyl-β-functionalized amides. Carbonyl addition products were formed when hindered alkenic esters were used.

We have previously reported on the rapidity with which a carbamoylsilane (**1**) reacts with electrophilically substituted acetylenes to afford a π-bond addition product or, accompanied by rearrangement, a C−H insertion product.[1] Electrophilically substituted alkenes have now been examined in order to compare ene/yne reactivity and possibly extend the scope of these additions to the production of silylated, vicinally difunctional alkanes (**2**). The latter are expected to be valuable synthetic intermediates, as treatment with flouride ion sources would allow them to behave as α-functionalized carbanions which could be captured by a variety of electrophiles.[2] Alternatively, simple protonolysis would afford products of overall hydroamidation. The alkene hydroamidation approach to amides is rare in the chemical literature, and as reported, is restricted to the use of electron-rich alkenes.[3]



1a, ***Si*** = TMS
1b, ***Si*** = TBS

2

Table 1 summarizes our results. Initial experiments involved **1a**,[4] but the need to stabilize hydrolytically sensitive adducts led us to later use the *tert*-butyldimethylsilyl analogue **1b** in some instances. Fortuitously, it was found that, besides generating products more stable to desilylation, **1b** was more reactive than **1a** in many instances. The overall tenor of the reaction with alkenic substrates is given by the data of entry 1, which indicates that the behavior of ethyl acrylate is quite different than that of the previously investigated[1] methyl propionate, both in reactivity and in outcome. Thus, no product of C−H "insertion" was found, and only slow addition to the double bond by **1a** was observed, although a reasonable yield of adduct **2a** was eventually obtained.[5] Similar behavior was observed by

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[1] Cunico, R. F. *Tetrahedron Lett.* **2001**, *42*, 2931−2932.

[2] For examples of how α-silylcarbonyl compounds have been used in this regard, see: Larson, G. L. *Advances in Silicon Chemistry*; JAI Press: Greenwich, 1996; Vol. 3, pp 243−249.

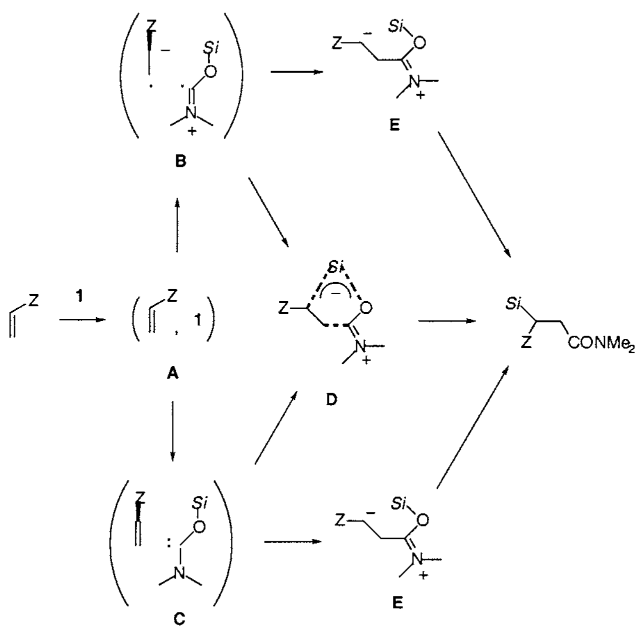
[3] (a) Keck, G. E.; Grier, M. C. *Synlett* **1999**, 1657−1659. (b) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369−378 and references therein. Ruthenium-catalyzed hydroamidations of alkenes are known, but mixtures of regioisomers are generally obtained: (c) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687−2690. (d) Kondo, T.; Okada, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 4123−4127. (e) Tsuji, Y.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1986**, *309*, 333−344.

[4] Cunico, R. F.; Chen, J. *Synth. Commun.* **2003**, *33*, 1963−1968.

[5] Attempts to enhance the rate of addition by the use of oxophilic catalysts such as $Yb(OTf)_3$ (100 °C, 18.5 h) or $Sc(OTf)_3$ (100 °C, 4.5 h) led to disappearance of **1a**, but no addition product was formed.

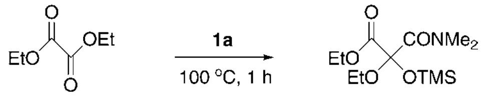
10.1021/ol040066p CCC: $30.25

Scheme 1



employing **1b**, but the reaction was accelerated, and **2b** was obtained in less than half the time required for formation of **2a** (entry 2). Alkyl- or aryl-substituted acrylic esters were less reactive than the parent. Methyl methacrylate gave no addition product with **1a** after 90 h at room temperature, but the use of **1b** did result in slow addition (entry 3). However, examination of the spectral data associated with this product indicated that it was exclusively one isomer of silyl ketene acetal **3a**.

Butyl cinnamate slowly formed an addition product from **1b** (entry 4) but exhibited yet another reaction mode, as the sole product was the mixed acetal **4a**, the result of addition to the carbonyl group of the ester. Although we have previously shown that a carbamoylsilane will add to ketones,[6] this is the first indication that ester carbonyls may be brought into play. We have briefly examined several nonalkenic esters for this mode of reactivity. No reaction occurred between **1a** and ethyl benzoate, but diethyl oxalate did afford an adduct **6**. The ease of addition may thus parallel increasing electrophilicity of the ester carbonyl moiety.



6, 76%

In an attempt to overcome the apparent blocking effect of the β-phenyl group, the doubly activated diethyl benzylidenemalonate was treated with **1b** and now displayed alkene addition (entry 5). However, the initial product was too sensitive toward desilylation to be completely characterized and was desilylated (CsF/EtOH) to give **5a**. The reaction of **1a** with diethylfumarate afforded not only the expected addition product **2c**, but also the ester carbonyl addition product **4b** in, respectively, a 2:1 ratio. NMR monitoring showed that this ratio was established early in the reaction and was invariant as time went on. Lowering the reaction temperature had little if any effect on this distribution. Although significant desilylative loss occurred upon chromatographic separation, characterization of both species was possible. Virtually identical results were obtained when the corresponding *cis*-alkene, diethylmaleate, was employed. Early aliquots of the reaction showed the presence of mostly diethyl maleate, together with smaller amounts of the fumarate, but the only addition products were again **2c** and **4b**, obtained in the same 2:1 ratio. Both cis and trans starting alkenes therefore led to the same mixture of the same chemo- and stereoisomers. Although maleate to fumarate isomerization may be occurring, with the reaction rate of the fumarate being much greater than that of the maleate, another possibility is that both fumarate and maleate proceed through a common intermediate before the configurations of the products are established. The absence of any diastereomer of **2c** indicates that the overall alkene addition is highly stereoselective.

The final conjugated ester employed ethyl 2,3-butadienoate was exceptionally reactive, leading to addition product some 36 times faster than ethyl acrylate (entry 7). The products, although inseparable, were identified as a 3:2 mixture of the conjugated silyl ketene acetals **3b** and **3c**. It thus appears that the presence of sp hybridization in the π-acceptor (allene, acetylene) is an accelerative factor in the addition reaction.

Turning to alkenes bearing other functionalities, the reaction of ethyl vinyl ketone with **1b** produced exclusively only one stereoisomer of the silyl enol ether **7**, the product of alkene addition (entry 8). Since saturated and aromatic ketones are known to undergo carbonyl addition under these conditions,[6] the chemoselectivity displayed here is quite striking. α,β-Unsaturated nitriles were next investigated, beginning with the reaction of acrylonitrile with both **1a** and **1b** (entries 9, 10). The products obtained were the vicinal alkene adducts **2d** and **2e**. These two reactions were used to determine more accurate relative reactivities of **1a** and **1b**,[7] affording values of $t_{1/2} = 5.5$ h for **1a** and 3.6 h for **1b**. A striking acceleration was observed when α-chloroacrylonitrile was employed with **1a** (entry 11) to form the alkene adduct **2f**. However, the combination of 1, 1-dichloroethene and **1b** showed no change after 48 h at 100 °C, indicating the importance of the conjugated functionality. The reaction of benzilidene malononitrile with **1b** was rapid compared to its diester counterpart (compare entries 5 and 12), but the initial adduct was again sensitive to protonolysis, and the desilylated product **5b** was obtained.

Product instability was also encountered in the addition of **1a** to 2-nitropropene (complete in 30 min at 70 °C).

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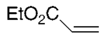
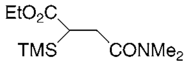
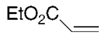
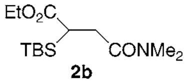
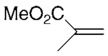
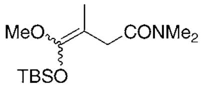
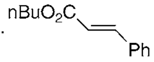
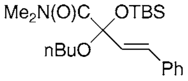
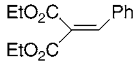
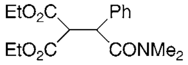
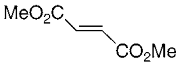
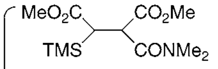
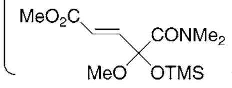
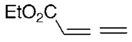
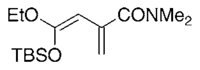
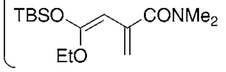
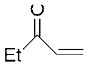
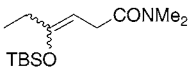
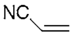
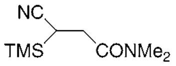
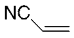
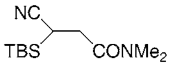
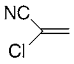
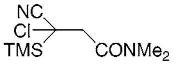
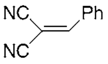
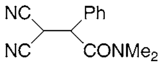
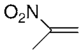
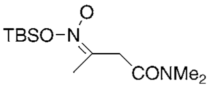
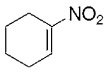
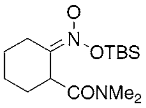
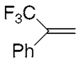
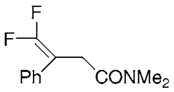
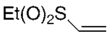
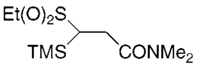
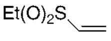
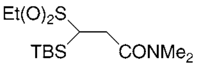
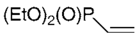
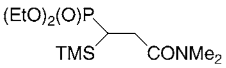
(6) Cunico, R. F. *Tetrahedron Lett.* **2002**, *43*, 355−358.

(7) Carried out in perdeuterobenzene at 75 °C in the NMR spectrometer with toluene as internal standard.

(8) Rapid exchange of the silyl group between the two oxygen atoms occurs: Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697−710.

(9) For an excellent review of reactions proceeding by SET pathways, see: Rathore, R.; Kochi, J. K. *Adv. Phys. Org. Chem.* **2000**, *35*, 193−318.

Table 1. Addition of **1a** and **1b** to Alkenes[a]

entry (alkene)		time	product	yield (%)
1. 	**1a**	45 h	 **2a**	74
2. 	**1b**	18 h	 **2b**	65
3. 	**1b**	63 h	 **3a**	65
4. 	**1b**	10 days	 **4a**	31
5. 	**1b**	10 h	 **5a**	40
6. 	**1a**	8 h[b]	 **2c**  **4b**	79
7. 	**1b**	0.5 h	 **3b**  **3c**	57
8. 	**1b**	16 h[b]	 **7**	60
9. 	**1a**	8 h	 **2d**	80
10. 	**1b**	4h	 **2e**	86
11. 	**1a**	0.5 h	 **2f**	65
12. 	**1b**	1.5 h	 **5b**	53
13. 	**1b**	15 min[b]	 **3e**	79
14. 	**1b**	2 h[b]	 **3f**	46
15. 	**1a**	7 days	 **8**	64
16. 	**1a**	4 h	 **2g**	77
17. 	**1b**	2 h	 **2h**	87
18. 	**1a**	14 days	 **2i**	84

[a] In toluene, 100 °C, 0.2 M, 1.2 equiv of **1**. [b] In benzene, 75 °C.

Removal of solvent quickly led to darkening of the sample, but the product (**3d**, see experimental**)** was stable in solution and displayed NMR data consistent with the expected nitronate structure.[8] Further confirmation of structure was obtained by protodesilylation to give *N*,*N*-dimethyl-3-nitrobutanamide. In contrast, utilizing **1b** led to a stable silyl nitronate (**3e**, entry 13), which could be fully characterized. The facility of addition to this monosubstituted alkene (compare entries 3 and 4) led us to examine the α,*β*-disubstituted nitroalkene shown in entry 14 which, although of lower reactivity as expected, easily afforded product **3f**. The nitro group thus appears to be a premier activating functionality for the addition reaction. **1a** slowly reacted with α-trifluoromethylstyrene (entry 15), but concomitant defluorosilylation (*β*-elimination) occurred to give difluoroalkene **8**. Entries 16 and 17 indicate that the sulfone moiety is only second to nitro as the best activating group. In contrast, diethylvinylphosphonate was the least reactive substrate, although a good yield of adduct **2i** was eventually realized (entry 18).

There are two mechanistic pathways currently under consideration for the additions of **1** to electrophilic alkenes: a process initiated by a single electron transfer (SET)[9] from **1** to the alkene or one in which a nucleophilic carbene derived from **1**[10] acts as a two-electron donor. We presently do not have definitive evidence for either of these possibilities, both of which are presented in Scheme 1 (*Si* = TMS or TBS). A donor-acceptor complex (**A**) is envisioned as a possible common precursor to both pathways, followed by SET to charge-transfer complex **B** or reorganization of **1** to the nucleophilic carbene **C**[11] (parentheses indicate closely paired, solvent-caged species). Depending on the degree of bond formation,[12] these pathways could be envisioned as having a commonality at **D** or at **E**, either of which can collapse to the observed products. Several observations have relevance to these and other mechanisms which could be postulated. (1) A $t_{1/2}$ NMR run between **1b** and acrylonitrile in benzene at 70 °C, but with the addition of one equivalent of TEMPO, gave a value of 2.5 h, a somewhat faster pace than in its absence. Additionally, no absorptions other than those of **2e** were seen in the NMR spectrum, and a preparative run gave **2e** uncontaminated with any possible TEMPO trapping product. Clearly, no radical chain process or contact-free radical species are involved in the overall addition. (2) Carbene **C** could be in equilibrium with **1**, and even in undetectable concentrations, provide a channel to products through *preformed* carbene. However, spectral data indicated that **1a** is stable at 200 °C for 2 h, with no evidence for a carbene coupling product.[13] We also note the report[14] that although photolysis of benzoyltrimethylsilane in the presence of silanes containing the Si−H bond afforded good yields of (trimethylsiloxy)phenylcarbene "insertion" products, no change in the benzoyltrimethylsilane occurred under photolysis *if the silane co-reactant was omitted.* (3) The dipolar intermediate which would arise from "conjugate addition" of the nucleophilic carbene to the alkene acceptor may also be reasonably postulated to have a cyclopropane precursor, but we have seen no evidence of such a cycloadduct upon periodic NMR monitoring of any of the additions reported here, including the closely followed $t_{1/2}$ experiments. Nor are we aware of any stable geminal aminooxycyclopropanes derived from electrophilic alkenes.[15] (4) The observation that **1b** reacts faster than **1a** excludes the possibility that silyl group transfer is involved in the rate-determining step of the additions. We presently entertain two explanations for this rate disparity. One is that the silyl group in **1b** is more electropositive than that in **1a** due to the substitution of the *tert*-butyl group for the methyl group. Determination of the ionization potentials[16] for the two carbamoylsilanes gave the values of 8.60 eV for **1a** and 8.47 eV for **1b**. This difference would coincide with both the SET and carbene arguments, since both transformations of **1** would be accelerated by a Si−C/Si−O bond[17] of higher electron density. Another possibility is that larger silyl groups may accelerate the isomerization of **1** (or its radical cation) to a siloxy form due to steric compression within the carbamoylsilane framework. This effect is under further investigation. In either case, it may well be that the concentration of initial "reactive pairs" controls the rate of the reaction.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] A formal carbene trapping product has been isolated from the reaction of **1a** and sulfur (Cunico, R. F.; Maity, B. C. *Org. Lett.* **2003**, *5*, 4947−4949); however, the observed carbene-like C−H bond insertion of a carbamoylsilane with methyl propynoate (vide supra) has so far not been seen when preformed nucleophilic carbenes were employed with this ester (dialkoxycarbene: Pole, D. L.; Sharma, P. K.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1335−1340; aminoalkoxycarbene: Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214−4215).

[11] *Acyl*silanes afford products attributable to silyloxycarbene intermediates under photolysis (Brook, A. G.; Kucera, H. W.; Pearce, R. *Can. J. Chem.* **1971**, *49*, 1618−1621) and thermolysis (Bassingdale, A. R.; Brook, A. G.; Harris, J. *J. Organomet. Chem.* **1975**, *90*, C6−C8).

[12] Silicon−carbon bond formation may be advanced in the case of **B**, while carbon−carbon bond formation may precede silyl group transfer if **C** acts as a nucleophile. The former is seen as analogous to mechanisms descibing initial proton transfer followed by radical−radical coupling in radical anion/radical cation pairs: Moss, R. A.; Platz, M. S.; Jones, M., Jr. *Reactive Intermediate Chemistry*; Wiley-Interscience: New Jersey, 2204; pp 242−243.

[13] Thermal generation of dialkoxycarbenes results in coupling products: (a) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751−8752. (b) Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443−4444. Some evidence exists for the dimer of an aminoalkoxycarbene: Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1264−1280.

[14] Watanabe, H.; Kogure, T.; Nagai, Y. *J. Organomet. Chem.* **1972**, *43*, 285−291.

[15] A geminal siloxy(*alkyl*)cyclopropane has been isolated from the photolysis of an acylsilane in the presence of diethyl fumarate: Brook, A. G.; Kucera, H. W.; Pearce, R. *Can. J. Chem.* **1971**, *49*, 1618−1621.

[16] He(I) photoelectron spectroscopy.

[17] The ground state of the analogous acylsilanes has been described as involving strong mixing between the oxygen lone pair and the silicon−carbon *σ* bond, thus leading to a lower ionization potential relative to all-carbon ketones: (a) Ramsey, B. G.; Brook, A.; Bassingdale, A. R.; Bock, H. *J. Organomet. Chem.* **1974**, *74*, C41−C45. (b) Yoshida, J.; Itoh, M.; Matsanuga, S.; Isoe, S. **1992**, *57*, 4877−4882.